improvement. Second, constructive engagement of and ownership by the entire critical care community is essential in developing a deliverable formula for change that need not be complex: the UK template comprised only 32 pages (16). Third, the principles of transparency and fairness must guide the allocation of what are, in any health care system, necessarily limited resources. Finally, political expediency must be countered by clinical need and a patient-centered, evidence-based approach.

***Author Disclosure*:** Neither of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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## References

1. Monthly NHS Hospital and Community Health Service (HCHS) Workforce Statistics in England–April. 2011 (accessed September 7, 2011). Available from: http://www.ic.nhs.uk/statistics-and-data-collections/workforce/nhs-staff-numbers
2. Provisional Monthly Hospital Episode Statistics for Admitted patient care, outpatient and Accident & Emergency data April 2010 to March 2011 (accessed September 7, 2011). Available from: http://www.hesonline.nhs.uk/Ease/ContentServer?siteID=1937&categoryID=1122
3. Davis K, Schoen C, Stremikis K. Mirror, mirror on the wall: how the performance of the US health care system compares internationally, 2010 update. New York: The Commonwealth Fund; 2010.
4. Secretary of State for Health. Equity and excellence: liberating the NHS. Department of Health 2010 (accessed September 7, 2011). Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117353
5. Public Accounts Committee–Forty-Fifth Report. The National Programme for IT in the NHS: an update on the delivery of detailed care records systems (accessed September 7, 2011). Available from: http://www.publications.parliament.uk/pa/cm201012/cmselect/cmpubacc/1070/107002.htm
6. Edwards N. The triumph of hope over experience: lessons from the history of reorganization (accessed September 7, 2011). London: NHS Confederation; 2010. Available from: http://www.nhsconfed.org/Publications/Documents/Triumph_of_hope180610.pdf
7. Walshe K. Reorganisation of the NHS in England. *BMJ* 2010;341:c3843.
8. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010;376:1339–1346.
9. Department of Health. Critical care beds (accessed September 7, 2011). Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Statistics/Performancedataandstatistics/Beds/DH_077451
10. Hutchings A, Durand MA, Grieve R, Harrison D, Rowan K, Green J, Cairns J, Black N. Evaluation of modernisation of adult critical care services in England: time series and cost effectiveness analysis. *BMJ* 2009;339:b4353.
11. Speciality Group for Critical Care. National institute for health research (accessed September 7, 2011). Available from: http://www.crncc.nihr.ac.uk/about_us/ccrn/specialty/critical_care
12. Intensive Care Audit and Research Centre. (accessed September 7, 2011). Available from: https://www.icnarc.org/
13. Faculty of Intensive Care Medicine. (accessed September 7, 2011). Available from: http://www.ficm.ac.uk/
14. Competency-based training in intensive care in Europe (accessed September 7, 2011). Available from: http://www.cobatrice.org/
15. Intensive Care Society. Available from: http://www.ics.ac.uk/
16. Working Party. Comprehensive critical care: a review of adult critical care services. London: Department of Health; 2000.
17. Wunsch H, Angus DC, Harrison DA, Linde-Zwirble WT, Rowan KM. Comparison of medical admissions to intensive care units in the United States and UK. *Am J Respir Crit Care Med* 2011;183:1666–1673.
18. Department of Health. The national education and competence framework for advanced critical care practitioners, 2008 (accessed September 7, 2011). Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_084011
19. Quality accounts. 2010/11 (accessed September 7, 2011). Available from: http://www.dh.gov.uk/en/Healthcare/Qualityandproductivity/Makingqualityhappen/qualityaccounts/index.htm


**DOI: 10.1164/rccm.201108-1414ED**

# Health Effects of Oil Spills: Lessons from the *Prestige*

Oil spills are not uncommon; on average, one major spill occurs each year (1). They mobilize large numbers of emergency responders to clean up the oil, typically involving a large manual effort. The consequences of oil spills are usually evaluated in terms of environmental damage, effects on marine species, and economic losses in the fisheries and tourism industries. Relatively little is known about their impact on human health.

Recently, attention to oil spills and their potential effects increased due to the Gulf of Mexico oil spill in the United States. Between April and July 2010, almost 5 billion barrels of crude oil were released after the explosion and sinking of the *Deepwater Horizon* drilling platform (2, 3). More than 100,000 persons, including professionals and community workers, have been involved in cleanup operations. A large epidemiological study is being set up to investigate potential health effects associated with cleanup activities following this spill. The design, methodology, and organization of this large effort may benefit from the experience obtained from previous studies (4).

In the last two decades, potential health effects of eight major oil tanker spills have been evaluated through epidemiological studies on residents, cleanup workers, or both, and have been summarized in recent reviews (1–3, 5, 6). Most of these studies provided evidence for an association between exposure to the oil spill and the appearance of acute physical, psychological, genotoxic, and endocrine effects in exposed populations. However, most of the studies had a cross-sectional design and small sample sizes, collected only self-reported health information, or had other methodological flaws hampering proper interpretations. Long-term health effects have been addressed on very few occasions.

The wreckage of the oil tanker *Prestige* off the coast of northwestern Spain in 2002 resulted in a major spill of about 67,000 tons of bunker oil. More than 300,000 people were involved in cleanup activities. During the first weeks of the disaster, cleanup work was predominantly performed by local fishermen without appropriate personal protective equipment. Potential effects of the *Prestige* oil spill on human health were evaluated in a number of epidemiological studies (1). The large-scale longitudinal study project promoted by the Spanish Society of Respiratory Medicine (SEPAR) (7, 8) aimed at evaluating long-term respiratory health effects and chromosomal damage in fishermen who participated in cleanup activities of the *Prestige* oil spill.

A questionnaire survey conducted in more than 6,000 affiliates of 38 fishermen's cooperatives showed that participation in cleanup work was associated with an increased prevalence of lower- and upper-respiratory tract symptoms, reported more than 1 year after active exposure (7). This association was linked to various types of cleanup activities and the risk increased with the degree and duration of cleanup effort, and with a less frequent use of face masks. The latter indicated that inhalation was a relevant exposure route and suggested that relatively simple control measures may reduce health hazards.

Fishermen were re-interviewed in a nested follow-up study 1.5 to 2 years after cleanup work, and it was found that respiratory symptoms were still more prevalent among fishermen highly exposed to oil, as compared with unexposed individuals (8). In addition, to explore mechanisms and to provide evidence using objective respiratory health endpoints, functional and biological tests were performed in strategic subsamples of exposed and unexposed individuals. While effects on conventional spirometric indices of lung function were not apparent, there was evidence of increased nonspecific bronchial responsiveness among the exposed, a finding that is compatible with the assumed airway irritation reflected by increased respiratory symptoms.

In this study, a considerable effort was placed on the determination of biological markers of effect in exhaled breath condensate (EBC). Levels of the oxidative stress marker 8-isoprostane were higher in cleanup workers, particularly among those who reported respiratory symptoms, as compared with nonexposed individuals. This suggested a potential involvement of oxidative stress as a mechanism of airway damage. In addition, the levels of two growth factors in EBC were higher among the exposed, a finding that may be indicative of a lasting airway remodeling process. Although the clinical significance of these observations is uncertain, the study highlights the applicability of EBC analysis in epidemiological studies.

In various studies on cleanup workers of the *Prestige* oil spill, potential genotoxic effects have been evaluated. A number of studies observed early effects on DNA during active exposure to the oil spill by using micronucleus tests, comet assay, and sister chromatid exchange (1). A higher risk of structural chromosomal alterations in circulating lymphocytes was found among fishermen 1.5 to 2 years after exposure (8). Although several of these biomarkers have been associated with an increased risk of developing cancer, the predictive values are largely unknown. A follow-up of both cleanup workers and unexposed individuals, including a repeated assessment of chromosomal damage 5 years after cleanup work, is currently underway.

The experience from studies related to the *Prestige* oil spill may be helpful for ongoing and future epidemiological studies on the health effects of oil spills (9). Exposures should be assessed as soon as possible after the disaster and during active cleanup work (10). Recruitment of study participants during cleanup work and a continuous recording of cleanup activities are very valuable. Since there is evidence that effects may persist after exposure, it is important to study long-term health effects, preferably in longitudinal studies. A variety of health endpoints should be considered, including endocrine, respiratory, cardiovascular, genotoxic, hematological, dermatological, neurobehavioral, carcinogenic, immunologic, renal, and reproductive effects. Although the clinical and public health relevance may often be uncertain, we strongly recommend the inclusion of biomarkers in addition to clinical and functional tests. Because it is often not feasible to study cancer as an endpoint, the determination of markers of early genotoxic effects is highly relevant. Long-term follow-up of large populations of exposed individuals is needed to understand whether there is an increased risk of cancer (9).

The clinical evolution of the observed effects, including respiratory symptoms and biomarkers, is uncertain. They may disappear, persist without apparent pathologic alterations, or evolve into a clinically apparent disorder that is at present unpredictable. Therefore, a continuous surveillance and follow-up of cleanup workers by health authorities is recommended.

Finally, because oil spills will occur again in many areas of the world, there is a need for a concerted, international action regarding human health effects. Although every spill has unique characteristics, common guidelines for preventive measures, the design of studies on the evaluation of long-term health effects, and surveillance of exposed cleanup workers and residents are necessary. Lessons from recent studies clearly indicate that potential health consequences in individuals exposed to oil spills can no longer be ignored.

***Author Disclosure***: F.P.-R.'s institution has received a grant from the Health Research Fund. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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## References

1. Aguilera F, Méndez J, Pásaro E, Laffon B. Review on the effects of exposure to spilled oils on human health. *J Appl Toxicol* 2010;30:291–301.
2. Solomon GM, Janssen S. Health effects of the Gulf oil spill. *JAMA* 2010; 304:1118–1119.
3. Goldstein BD, Osofsky HJ, Lichtveld MY. The Gulf oil spill. *N Engl J Med* 2011;364:1334–1348.
4. Weinhold B. Emergency responder health: what have we learned from past disasters? *Environ Health Perspect* 2010;118:a346–a350.
5. Rodriguez-Trigo G, Zock JP, Isidro I. Health effect of exposure to oil spills. *Arch Bronconeumol* 2007;43:628–635.
6. Ha M, Lee WJ, Lee S, Cheong HK. A literature review on health effects of exposure to oil spill. *J Prev Med Pub Health* 2008;41:345–354.
7. Zock JP, Rodríguez-Trigo G, Pozo-Rodríguez F, Barberà JA, Bouso L, Torralba Y, Antó JM, Gómez FP, Fuster C, Verea H. Prolonged respiratory symptoms in fishermen who participated in clean-up activities of the *Prestige* oil spill. *Am J Respir Crit Care Med* 2007;176:610–616.

8. Rodríguez-Trigo G, Zock JP, Pozo-Rodríguez F, Gómez FP, Monyarch G, Bouso L, Coll MD, Verea H, Antó JM, Fuster C, *et al*. Health changes in fishermen 2 years after clean-up of the *Prestige* oil spill. *Ann Intern Med* 2010;153:489–498.
9. Savitz DA, Engel LS. Lessons for study of the health effects of oil spills. *Ann Intern Med* 2010;153:540–541.
10. Cullinan P. Epidemiological assessment of health effects from chemical incidents. *Occup Environ Med* 2002;59:568–572.


**DOI: 10.1164/rccm.201102-0328ED**

# Reslizumab and Eosinophilic Asthma: One Step Closer to Phenotype-directed Therapy?

The idea that asthma represents a single disease has been replaced with the belief that it instead represents a heterogeneous mix of overlapping syndromes. Classically defined by the clinical presentation of intermittent respiratory symptoms accompanied by reversible airflow obstruction, nonspecific bronchial hyperresponsiveness, and airway inflammation, clinicians now recognize that multiple distinct phenotypes actually exist within this condition. Numerous strategies have been proposed for categorizing these phenotypes based on clinical or physiologic characteristics, response to potential environmental triggers, or airway inflammatory cell profiles (1–4). As we move our classifications away from the more traditional clinical descriptions to include a more multidimensional emphasis on cellular biology and subphenotypes, we increase our opportunities to provide phenotype-directed therapies, especially in more severe disease. Historically, the presence of eosinophilic inflammation has been the most useful way to predict response to therapy in asthma (5). However, new approaches that have focused on molecular phenotyping (6) and noninvasive biomarkers (7) have also shown promise in predicting response to treatment.

The availability of two monoclonal antibodies directed against interleukin-5 (IL-5), mepolizumab and reslizumab, has provided an opportunity to investigate the role of this pathway in defining specific targets for asthma therapy. In this issue of the *Journal*, Castro and coworkers (pp. 1125) add to the growing body of evidence that suggests that the accurate definition of asthma phenotypes is critical in selecting targets for investigational therapies, ultimately providing the basis for targeted treatment and phenotype-specific asthma care (8). In patients with poorly controlled asthma and sputum eosinophilia, administration of the monoclonal antibody to IL-5, reslizumab, resulted in a reduction in sputum and blood eosinophils counts and a statistically significant yet modest improvement in pulmonary function when compared with placebo after 15 weeks, and failed to improve asthma control (as measured by the Juniper Asthma Control Questionnaire [ACQ]) in the population as a whole. There was a trend toward decreased exacerbations with reslizumab, but exacerbations were infrequent in both the treatment and placebo groups, and the short duration of the study limited the ability to fully evaluate this potential effect.

In subgroup analyses, the response to therapy seemed to be greater in those with a history of nasal polyposis, where the authors noted an improvement in ACQ from baseline to end of therapy in the reslizumab group. However, the improvement noted in pulmonary function testing did not differ between those patients with and without nasal polyps. Castro and colleagues suggest that in patients with uncontrolled, eosinophilic asthma, the presence of nasal polyps may help identify a subset of patients who may benefit the most from anti–IL-5 therapy, but this will need to be specifically investigated in future studies.

Despite the modest clinical benefits noted, the trial was not without limitations. Because the study was not designed to specifically investigate the relationship between nasal polyps and response to anti–IL-5 therapy, it is not possible to fully evaluate this association or the possible underlying mechanisms. In this small sample size of 53 subjects, 22 were identified as having nasal polyps, but no standardized method for confirming the diagnosis was required and objective scoring systems for characterizing the polyps were not included. Possible confounding factors, such as the presence of aspirin-exacerbated airway disease or the use of leukotriene receptor antagonists in the nasal polyp group, were not considered. Finally, the inclusion of exhaled nitric oxide as a marker of eosinophilic inflammation or changes in serum and tissue levels of IL-5 in response to treatment would have been beneficial.

While the relationship between nasal polyposis, asthma, and potential benefit from anti–IL-5 treatment will need to be better defined, there is evidence to support this initial observation. The presence of eosinophilic inflammation provides the basis for a common pathologic mechanism between the two conditions (9, 10) where patients with asthma and nasal polyps have been shown to have greater densities of eosinophilia in nasal polyps compared with patients without asthma (9), and patients with nasal polyps and nonspecific bronchial hyperresponsiveness have been observed to have eosinophilic inflammation of the lower airways that resembles that seen in patients with asthma (10). In addition, levels of IL-5 in nasal secretions have been shown to predict response to IL-5 blockade, where anti–IL-5 therapy has been shown to reduce the size of nasal polyps in a subset of patients with elevated nasal concentrations of IL-5 (11). Interestingly, though, nasal IL-5 levels have been shown to actually increase in nonresponders with nasal polyps despite a similar reduction in circulating blood eosinophils (11), again highlighting the need to precisely identify the appropriate target population for therapy even in the presence of nasal polyps. Whether this could have contributed to the increase in reported symptoms of nasopharyngitis in the current study (8) will need further exploration.

Also of interest is the observation that in patients with asthma, there appears to be a similar differential effect of anti–IL-5 blockade in various tissue compartments, where mepolizumab has been shown to reduce blood and sputum eosinophilia by nearly 100% but only 55% in the bronchial mucosa (12). As discussed by Flood-Page and colleagues (12), it is possible that varying degrees of tissue penetration, altered receptor expression, or receptor down-regulation could be responsible for these disparate effects, ultimately leading to differences in clinical responses. Similarly, one must consider that IL-5 may not act alone to promote the recruitment and survival of eosinophils in the tissues. Preliminary evidence suggests that eotaxin, granulocyte/macrophage colony-stimulating factor (GM-CSF), or interleukin-3 (IL-3) may all play a role in eosinophil viability in the tissues (13).

Castro and colleagues have expanded the current body of literature (8) evaluating the safety and effectiveness of anti–IL-5 antibodies, where the presence of eosinophilic inflammation seems to best predict response to therapy. In early studies in asthma in which participants were not selected on the basis of